Pediatric Lymphoma Patients: Cytomegalovirus Infection

15

Samah A. Loutfy

Contents

Abstract

Cancer care has improved and intensified over recent decades, and as patients with cancer survive longer, various infectious complications have been more pronounced. Pediatric cancer patients are at high risk of infectious complications because they are immunologically immature. Human cytomegalovirus (HCMV) is a persistent pathogen, can cause life threatening infection in immunocompromised patients, such as bone marrow and organ transplant recipients, persons with AIDS, and patients with hematological malignancies (leukemias and lymphomas). Despite Previous studies before application of sensitive molecular methods, demonstrated association of CMV with fever and hepatitis in children with malignancy, CMV has not been extensively studied in pediatric cancer patients. Very limited data are available in the literatures related to symptomatic CMV infection and its clinical relevance on outcome of diseases in pediatric cancer patients especially children with hematological malignancies. These studies are relevant as new advanced diagnostic techniques are now available for detection of the virus in different clinical specimens, new advances in the management of CMV infection and disease have been developed, and the performance of prospective clinical trails of antiviral agents has been evaluated. Therefore, the aim of this review is to shade a light on some of these data that are available

S.A. Loutfy (✉)
Virology and Immunology, Cancer Biology Department, National Cancer Institute, Cairo University, Giza, Egypt
e-mail: samaly183@yahoo.com

M.A. Hayat (ed.), *Pediatric Cancer, Volume 4: Diagnosis, Therapy, and Prognosis*, Pediatric Cancer 4,
DOI 10.1007/978-94-007-6591-7_15,

in the literatures, and relevance of future studies concerned activity of CMV in pediatric lymphoma patients.

Cytomegalovirus Background

Human cytomegalovirus (HCMV) is a DNA virus of the betaherpesviridae family, with a diameter of 200 nm, linear double stranded DNA is approximately 240 kb in size. It is the largest member of the herpesvirus family. It has unique long (UL) and short sequences (US), both of which are bounded by homologous repetitive sequences. It encodes about 200 open reading frames. Until now only 33 structural proteins and some infected cell proteins are known. CMV replicative cycle has been divided into three independent times periods-immediate-early (IE: defined 2–4 h post infection), early (E: 8–24 h post infection), and late (L 12–36 h post infection) based on the appearance of different classes of CMV-specific proteins during each interval. Expression of both E and late genes is dependent on IE gene expression (Sinclair and Sissons 2006). The first CMV infection in humans was probably recorded in the year 1881 by Ribbert (Vancíková and Dvorák 2001). Various strains of CMV, that can consequently infect the same patient, exist.

CMV infection is distributed worldwide, with geographic differences explained by socioeconomic differences of exposure. In developing countries where poor hygiene and overcrowdness, and low socioeconomic status, children acquire infection early in life, and seroprevalence approaches 100% by early adulthood. In contrast, in developed countries, the seroprevalence of CMV approximates 50% in young adults (Wang et al. 2011). Sources of virus include oropharyngeal secretions, urine, cervical and vaginal secretions, spermatic fluids, breast milk and blood. Vertical spread is transplacental. An important route of infection is iatrogenic-solid organ (SOT) and bone marrow transplantation (BMT) and blood transfusion (Vancíková and Dvorák 2001). Except for a mononucleosis-like illness in some persons, infection with CMV rarely causes disease in immunocompetent individuals. Therefore, CMV disease is restricted to the immunocompromised host (Vancíková and Dvorák 2001; Loutfy and Mansout 2000).

CMV has evolved several strategies to avoid its elimination and eventually hides itself in a silent state, referred as "viral latency" with absence of any detectable production of infectious virus, but kept the ability of viral genome to reactivate under specific stimuli. There is a possibility that CMV reactivation occurs routinely in normal, healthy virus carriers, but this is unlikely to present a problem in the immunocompetent, due to a robust CD8+ cytotoxic T-lymphocytes (CTL) response to the virus. Consistent with this is the observation that the T-cell repertoire of healthy seropositive individuals contains a strikingly high frequency of CTLs that recognize CMV epitopes. It is also still unclear whether any increased frequency of cells reactivating CMV from latency results from immunosuppression per se; reactivation itself could be stimulated greatly by numerous cytokines elicited by other infections, allogeneic stimulation, transplant rejection or graft-versus-host disease-all of which often result in, or are treated by, immunosuppression (Sinclair and Sissons 2006).

In vivo studies have demonstrated a particularly strong relationship between CMV and DCs and showed that persistence of CMV is associated intimately with the normal program of myeloid-cell differentiation; it is the changes in the internal cellular environment that accompany differentiation that promote virus reactivation.

Therefore, future studies will be needed to define precisely the biochemical triggers responsible for myeloid DC differentiation as these also appear to promote the switch from viral latency to reactivation (Sinclair and Sissons 2006).

Cytomegalovirus Infection in Patients with Hematological Malignancies

Cytomegalovirus continues to be a significant cause of morbidity and mortality in immunocompromised hosts, including those with human immunodeficiency virus (HIV) infection and patients following allogeneic stem cell transplantation

(SCT) or organ transplantation. The virus causes such CMV related diseases as pneumonia, enterocolitis, and retinitis, Ganciclovir and foscarnet are effective drugs for treating CMV caused disease, but they have various side effects, including pancytopenia and renal dysfunction. Moreover, inappropriate dosage regimens can lead to the appearance of drug resistant virus strains (Ikewaki et al. 2003).

T-cell function plays a crucial role in maintaining CMV in the latent stages and in controlling CMV infection. Therefore, patients with impaired cellular immunity such as leukemia or lymphoma are at higher risk for developing CMV antigenemia (A) and disease (D) due to insufficient lymphoid control (both humoral and cellular) (Han 2007; Torres et al. 2006). Furthermore, T-cell depleting agents (e.g. alemtuzumab) and aggressive chemotherapy (e.g. hyper-CVAD, and acute leukemia induction) appear to increase the risk of CMV infection and disease (Wade 2006). Reports about incidence of these infections in lymphoma patients have been limited to a few case reports, small case series, and postmortem studies (Torres et al. 2006; Han 2007). Epidemiological studies of CMV infection in cancer patients is important not only clinically for risk assessment and the timely diagnosis and treatment of the infection to allow better management of underlying cancers but also scientifically for better understanding of the virus-host interaction (Han 2007).

Incidence

In the absence of effective antiviral prophylaxis, the incidence of CMV infection among patients with hematological malignancy ranges from 5 to 75% (Wade 2006). An Early prospective surveillance study from the University of Maryland Cancer Center reported an incidence of CMV infection in patients with acute leukemia and ranged from 32 to 58% (Wade 2006). Non-SCT patients had an overall positivity rate of 9.3%, and those with lymphoid hematologic malignancies (CLL, lymphoma and ALL) were affected more than those with myeloid hematologic malignancies (13.6% versus 3.9%, $P<0.001$) (Han 2007; Ljungman et al. 2008). Investigators at the Medical Anderson Cancer Center have reported a series of retrospective studies on the incidence of CMV disease among patients receiving conventional therapy (Torres et al. 2006). Those investigators have reported an overall increase in CMV gastrointestinal disease and CMV pneumonia among patients with lymphoma and acute leukemia. These diseases were associated with high dose of cytarabine, fludarabine, or cyclophosphamide, and increased patient age. CMV attributable mortality for these patients ranged from 30% in lymphoma to 57% in leukemia and up to 90% in those undergoing HSCT (Torres et al. 2008; Wade 2006). Faderl and his co-workers have reported that CMV viremia was detected in 15% of patients with lymphoid malignancy who were treated with alemtuzumab and rituximab (Faderl et al. 2003). Viremia developed a median of 28 days after starting therapy (Wade 2006). Torres et al. (2008) have reported that incidence of CMV pneumonia in 20% of lymphoma patients was mainly in NHL (16% NHL versus 4% HL).

In contrast, another study (Chemaly et al. 2005) has reported that CMV pneumonia is less common among patients with lymphoma (1%: 1.2% in NHL versus 0.6% in HL patients) than among patients with leukemia (2.9%), or patients who have undergone autologous HSCT (2%), solid organ transplantation (17–90%), or allogeneic HSCT (7–20%). They reported that median time from diagnosis of lymphoma to onset of CMV pneumonia was 469 days (range 27–4,682 days) in patients with NHL and 135 days (range 40–275 days) in patients with Hodgkin disease ($P=0.020$).

Epidemiology in Pediatric Lymphoma Patients

Generally, pediatric cancer patients are different from their adults in spectrum of oncologic diagnosis, intensity of chemotherapeutic regimens, and incidence of co-morbid medical conditions preceding diagnosis of cancer (Koh and Pizzo

2011). They reported that some risk factors exacerbate immunocompromise state in pediatric cancer patients enhancing their susceptibility to infectious complications like: alterations in central nervous system function or decreased levels of awareness, obstruction of a hollow viscus, depressed nutritive states this besides maturity of immune system is related to age (Jones et al. 1996). They reported that mortality rate due to CMV pneumonia was higher among lymphopenic patients highlights the important role of lymphocytes in controlling viral infections (Nguyen et al. 2001).

Yee-Guardino et al. (2008) have added, however, that β-herpesviruses are known to be an important pathogens in immunocompromised patients, and they have not been extensively studied in children with malignancies. Children with leukemia have been reported to have a high frequency of active CMV infection (range, 27–46%). But a relatively low frequency of serious CMV disease (range, 3–5%) (Yee-Guardino et al. 2008).

Torres et al. (2008) have reported that CMV disease specific mortality rate reaches up to 30% in lymphoma patients. In our previous report, CMV infection have been detected in 34% of pediatric lymphoma patients (Loutfy et al. 2010). Most of CMV infection was among NHL patients of B subtype. This might be as reported previously due to exposure to more selective suppressive chemotherapy such as methotrexate, corticosteroids and cyclosporine that leads to diminished T cell function with disappearance of CD8 cytotoxic population (Chemaly et al. 2005). Recently, a retrospective study has been performed in Taiwan, showing that 29.9% of their hematological malignancy adult patients suffered from CMV viremia with a mortality rate of 43.8% (Wang et al. 2011).

Severity of CMV Disease

Serious CMV disease is especially high among patients with impairments in their cell mediated immunity. Disease manifestation varies in severity depending on degree of host immunosuppression. In patients with hematological malignancies CMV infection can cause a wide variety of disease manifestations, including fever, cytopenia, esophagitis, enterocolitis, hepatitis, cystitis, pneumonitis, retinitis, encephalitis, marrow suppression and disseminated disease. (Nguyen et al. 2001; Wade 2006). Pneumonitis, gastro-intestinal disease and retinitis are serious complications of CMV reactivation in patients with non-Hodgkin's lymphoma (Ducancelle et al. 2004). At MDACC, they observed that the frequency of serious CMV disease and of CMV pneumonia in particular among patients with hematological malignancies, escalated steadily during 1990s (Nguyen et al. 2001). Table 15.1 summarizes some of the most common clinical manifestations in patients with hematological malignancies.

Table 15.1 Clinical manifestations of CMV infection in patients with hematological malignancies

Clinical manifestations	Type of malignancy	Patients diagnosed/ patients reviewed (%)	Diagnostic test	Reference
Leukocytosis	Hematological malignancies	5/32 (15.6)	Real time PCR	Wang et al. (2011)
Neutopenia		13/32 (40.6)		
Lymphopenia		24/32 (84.4)		
Pneumonia	Adults with leukemia	61/2,136 (2.9)	Cell culture, IHC, histopathology	Nguyen et al. (2001) and Torres et al. (2008)
	Hematological malignancies	16/25 (64)		
Gastrointestinal	Hematological malignancies, and solid tumors	47/236,113	Cell culture, in situ hybridization, IHC, histopathology	Torres et al. (2006)
		15/47 were lymphoma		
Retinitis	CLL	Case report	PCR	Church et al. (2007)

Risk Factors Associated with CMV Disease

Some risk factors showed to be associated with CMV viremia and not only have an impact on outcome of cancer disease but also may be used in combination to identify patients at the highest risk of CMV disease in whom early intervention might be of greatest value (Meyers et al. 1990). They demonstrated that seropositive patients, older patients, patients with acute graft-versus-host disease were more likely to develop CMV pneumonia than were patients without these characteristics.

In the study of Wang et al. (2011), univariate analysis showed that mechanical ventilation, leukocytosis, hypoalbuminemia, and lack of appropriate early treatment were associated with higher mortality among patients with underlying diseases (hematological malignancy and solid tumors) suffering from CMV viremia. In the multivariate analysis, mechanical ventilation, leukocytosis, and lack of appropriate antiviral therapy were independent risk factors for mortality associated with CMV viremia in cancer patients. This indicates that CMV viremia had poor outcomes in cancer patients.

In another study, multiple logistic regressions identified complete remission and long duration of lymphopenia (>3 months) as independent factors associated with fatal CMV pneumonia in lymphoma patients (Torres et al. 2008). In addition, in their autopsy series they demonstrate other common factors that may be used to identify patients at risk of fatal infection, among these predictors, herpes simplex virus infection/reactivation that seemed to be a marker of presumptive cellular immunosuppression preceding the onset of CMV pneumonia in the study patients. Other previous studies have reported that HHV6 infection is one of the major contributions for induction of an immunosuppression state in patients with BMT and solid organ transplantation associated with active replication of CMV in blood compartment and affects both clinical picture and prognosis in those patients (Loutfy et al. 2010).

Chemaly et al. (2005) have reported some predictors of death due to CMV pneumonia in lymphoma patients on univariate analysis included, a high APACHE II (higher Acute Physiology and Chronic Health Evaluation II) score (>16), this may be as reported by Wang et al. (2011) due to leukocytosis which is a criterion of systemic inflammatory syndrome and have higher APACHE II score (Chemaly et al. 2005; Wang et al. 2011). Admission to ICU, lack of antiviral therapy, and development of toxicity to antivirals are other predictors of death due to CMVp. Using multivariate analysis, predictors of death due to CMVp were a high APACHE II score (>16) at onset of CMVp and development of toxicity to antivirals. Patients with high APACHE II score (>16) at onset of CMVp had 15.5 times the risk of dying of CMVp compared to patients with low APACHE II scores (Chemaly et al. 2005).

In an earlier study done by Torres et al. (2006), they have reported that mortality rate with CMV disease in lymphoma patients was 29%, they have identified several risk factors can predict fatal outcome of CMV antigenemia and or/CMV disease in such patients by univariate analysis included, admission to ICU, mechanical ventilation level of LDH, high antigenemia burden (median 133 infected cells /1,000,000 WBC's), active lymphoma disease (progressive disease), relapsed patients, advanced lymphoma stage (III/IV), and antiviral related toxicity. On multivariate analysis only antiviral related toxicity was independent predictor of fatal outcome of CMV antigenemia/or disease in lymphoma patients.

As regards age, sex, and ethnicity and their association with CMV viremia in lymphoma patients. Seroprevalence of CMV is age-dependent, ~about 58.9% of individuals at age of 6 and older are infected with CMV while 90.8% of individuals at age of 80 and older are positive for HCMV (Staras et al. 2006). In the study done by Wang et al. (2011) they observed that mean age of CMV viremic patients with solid organ malignancies was significantly younger than those with hematological malignancies (63 years vs 71.8 years, P=0.03). Torres et al. (2006) have reported that the majority of CMV viremic

patients were men. The median age was 60 years (range 17–87 years). These authors showed in the autopsy study that the median age of patients with CMV pneumonia in lymphoma patients was 43 years (15–76 years). Also, it has been reported that Asian patients with lymphoma and myeloid and other hematological diseases had significantly higher CMV antigenemia rates than whites. This may be explained by higher rates of CMV antibody among Asians and blacks than whites. This suggests the role played by host factors in CMV antigenemia rates and viral burden (Han 2007).

Association with Other Herpes Viruses

In our previous report, it has been observed that both CMV and HHV6 were present in 47% of pediatric NHL cases (Loutfy et al. 2010). Previous studies have addressed explanations for such observations which could be due to: (1) immunosuppression from both NHL disease and its treatment may predispose patients to higher risk of coinfection, (2) An immunomodulating effect of HHV6 since it can induce production of interleukin -1β and tumor necrosis factor- alpha, suppress T lymphocyte function due to reduced interleukin-2 synthesis, and suppress bone marrow by inducing interferon -alpha production. (3) HHV-6 can directly infect CD4+ T-cells and induce apoptosis, thus altering key immune activation molecules pathways and subsequently disturbing the cytokine network. (4) HHV-6 can also infect thymic epithelial cells, hematopoietic stem cells, and natural killer cells, which are critical for immune maturation and protection against cancer and viral infections.

All these factors could contribute to pathologic effects of CMV as a result of HHV6 reactivation, and also create an environment suitable for persistence of HHV6 latency (Wang et al. 2006). In addition, it has been reported that the combination of both HHV6 and CMV infection after organ transplantation was more likely to be associated with CMV disease than with CMV infection alone (Loutfy et al. 2010). Furthermore, our study extended to demonstrate adverse impact of presence both herpes viruses (HHV6, CMV) in pediatric lymphoma patients, as 70% of those patients showed clinical manifestations of severe chest infection and were associated with more frequent episodes of febrile neutropenia (median 3 episodes), long duration of febrile neutropenia > 10 days, absolute neutrophil count (ANC) of < 0.8, thrombocytopenia (plt < 96), and low Hb concentration (Hb < 9.1). However, these data are limited by interference of lymphoma treatment which could aggravate suppressive effect of presence of both herpes viruses (Loutfy et al. 2010).

A few clinical studies have investigated whether there is an association between CMV and Epstein-Barr virus (EBV) reactivation in the blood compartment of immunosuppressed patients. While they have been found that reactivation of each virus occurred independently, others have shown an association between CMV infection and the serologic profile of EBV reactivation. In vitro studies have shown as well that there might be an association between CMV and EBV (Bauer et al. 2007).

Laboratory Diagnosis for CMV Infection/Disease in Pediatric Lymphomas

Early and accurate diagnosis and reliable methods for monitoring CMV infection are essential for managing adult T- cell leukemia-lymphoma patients (Ikewaki et al. 2003).

The conventional methods for the diagnosis of CMV infection/disease are viral isolation by viral culture, serology which includes CMV specific antigen and antibody detection, molecular method for detection of viral DNA from blood and clinical specimens. Although serology is sensitive and specific, results are not helpful in immunocompromised cases because, (1) not rapid due to the need to obtain a convalescent serum sample 10–14 days after initial sample, (2) in certain types of immunocompromised patients, the ability to mount an IgM response may be impaired; therefore, IgM is not reliable for diagnosing active infection (Drew 1992).

Viral isolation done by either tissue culture or shell vial is the most specific diagnostic test and

till now was regarded the gold standard, but it is labor intensive and take time (24–48 h) till the results are available. Hence, other rapid methods such as detection of pp65 antigen from peripheral blood leukocytes (antigenemia assay) and CMV DNA are preferred for diagnosis (Jain et al. 2011). A valuable feature of the CMV antigenemia assay is that it is rapid (4–5 h), quantitative, antigenemia became positive 8± 7 days before onset of symptoms while antibody response observed 4 ± 9 days after onset of symptoms. Therefore, antigenemia test is useful in monitoring infection and antiviral treatment in immunocompromised patients, because high levels of antigen are frequently found in patients with CMV disease and low levels correlate with asymptomatic infections (Loutfy and Mansout 2000). However, there is disadvantage to this method, it couldn't distinguish between primary and reactivated infection (Vancíková and Dvorák 2001).

Molecular methods considered to be the relevant diagnostic methods for detection CMV DNA in various samples. PCR is highly sensitive and specific method that is now being applied in a quantitative or semi-quantitative manner. It has the ability to detect minute amounts of nucleic acid in various clinical samples, and can detect the onset of CMV viremia 1-2 week prior to culture and antigenemia tests. However, its inherent sensitivity poses a problem because latent CMV genomes, which are present in leukocytes of practically all seropositive individuals, may be amplified (Razonable et al. 2002).

Quantitation of CMV DNA

Quantitation of CMV DNA in plasma and other biological samples is very useful for rapid diagnosis of infection and effective monitoring clinical course of disease and response to therapy. Therefore, it can be used as an early indicator of development antiviral resistance as CMV DNA in the plasma tend to persist longer after therapy than pp65 antigens (Razonable et al. 2002). Preliminary data suggests that various clinical manifestations, such as prolonged fever, pneumonitis, heart failure, and retinitis, existed in immunocompromised patients with heavy viral burden (Han 2007). Difference between viral load among symptomatic patients when compared with asymptomatic patients in kidney transplant patients (KR) was reported. In study from Kuwait, they reported that median viral load (4.7log10 copies/ml) of symptomatic KR was significantly higher than that found among asymptomatic KR (2.2 log 10 copies/ml) (Madi et al. 2007). Such data are not available in the literatures, particularly in patients with malignancies with CMV infection and or /disease (Wang et al. 2011). However, as we mentioned before regarding data reported concerned antigenemia rate which is one of the risk factors for development of fatal outcome of CMV disease in lymphoma patients (median number of CMV infected cells per 1,000,000 WBCs was higher in patients with CMV-disease compared to those with antigenemia (median 18 vs 5 cells). Meyers et al. (1990) have reported that CMV viremia had a higher positive predictive value before the onset of CMV disease, particularly prior to pneumonia and gastrointestinal diseases. Prevention of the progression of CMV infection from asymptomatic excretion to symptomatic CMV disease depends on a number of factors like: (1) the interval between the first excretion and the onset of clinical disease, they reported that the median interval between CMV viremia and occurrence of CMV disease was 14 days which is sufficiently long to allow initiation of antiviral chemotherapy, (2) Rapid and higher test sensitivity, and (3) disease prevalence in seropositive patients. These data when combined with viral load might help clinician in the early identification of patients at high risk for fatal outcome due to CMV viremia and increase opportunity of early intervention in the course of infection before the onset of disease.

All possible definitions that related to diagnosis of CMV infection and disease have been published for application in immunocompromised patients and summarized in Fig. 15.1. They recommended that CMV syndrome which can cause fever and bone marrow suppression (neutropenia and thrombocytopenia), these symptoms can be associated with other causes in stem cell transplant recipients, including human

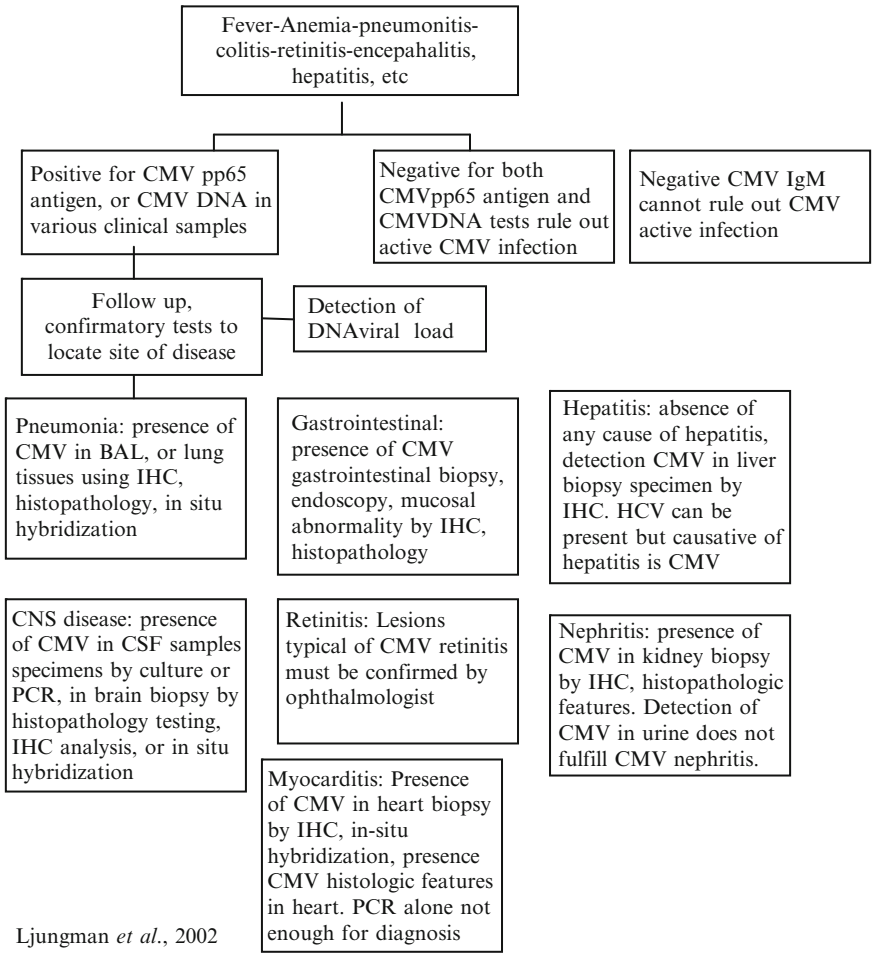

Fig. 15.1 Systematic approach for diagnosis of CMV infection/disease in immunocompromised host (Ljungman et al. 2002). *ICH* immunohistochemistry

herpesvirus 6 (HHV6). Therefore, term CMV syndrome can be used but at least after testing HHV6 and it is important that cases of CMV syndrome be differentiated from cases of end organ disease (Ljungman et al. 2002).

Treatment of CMV Infection/Disease in Immunocompromised Patients

The choice of antiviral drugs depends on; individual patient, risk of progression of CMV disease, and risk of side effects of chosen drug (Ljungman et al. 2008). Three major therapeutic approaches are currently employed to manage CMV infections and diseases; (1) prophylactic, (2) preemptive, and (3) disease treatment.

Prophylactic treatment. This strategy of treatment is started in the absence of detectable virus or disease, aimed to prevent CMV infection or reactivation in patients at risk of subsequently developing disease. The potential benefit of the prophylactic treatment is to prevent infection during 3–6 months after transplantation. Although this can decrease early CMV disease, the mortality rate was not changed because intercurrent

infections and high incidence of late CMV disease (Yeung et al. 2009). Ganciclovir administered intravenously (DNA polymerase inhibitor) for 2 weeks or for at least 3 months following transplantation, reduces risk of CMV disease but didn't improve survival as long lasting treatment was found to be associated with neutropenia and secondary bacterial and fungal infections (Ljungman et al. 2008). Valganciclovir is an effective oral formulation for treatment of CMV infection, is devoid of adverse side effects related to the use of i.v. ganciclovir, cidofovir and foscarnet (Cvetković and Wellington 2005). Foscarnet can be used as an alternative to i.v. ganciclovir in case of marrow suppression or development of resistance (Yeung et al. 2009). Immunoglobulins have no value in prophylaxis.

Preemptive treatment. This strategy was first documented in 1990s, requires the administration of antiviral drug only when patient develops laboratory evidence of CMV infection. In this regard, pre-emptive therapy is usually guided by routine monitoring of CMV infection such as the presence of viral DNA or antigens in the blood prior of the development of symptoms (Wang et al. 2011). Such strategy showed some advantages include: (1) target patients who are at high risk of developing infection and disease, (2) reduce antiviral toxicity, (3) reduce the chances of the emergence of drug resistant mutants, and (4) reduce the cost of treatment (Ljungman et al. 2008). Either i.v. ganciclovir or foscarnet can be used for first line preemptive therapy. Cidofovir can be considered for second line pre-emptive therapy with careful monitoring of renal toxicity. Valganciclovir might be used in place of i.v. agents in low risk patients (Ljungman et al. 2008). Clinical risk factors for CMV disease need to be well defined so that prophylactic and preemptive strategies can be targeted rationally (Nguyen et al. 2001)

Treatment of symptomatic CMV infections and diseases. In case of symptomatic infection, those are patients with CMV viremia (CMV DNA in blood) and showing symptoms compatible with CMV (fever with or without bone marrow suppression) but without signs of CMV end organ diseases, which should be carefully assessed. In SCT, i.v., ganciclovir or foscarnet can be administered as first line of treatment. In patients receiving alemtuzumab, valganciclovir is used in addition to ganciclovir and foscarnet (Ljungman et al. 2008). Failure of preventive strategies leads to development of CMV disease; such disease can develop anytime after SCT from early neutropenic phase up to several years after transplantation. Combination of i.v., gancyclovir and high dose of immunoglobulin is used for treatment of CMV pneumonia. No data support the administration of immunoglobulin for treatment of manifestations of CMV diseases other than pneumonia. Foscarnet might be used in place of ganciclovir. Cidofovir or combination of foscarnet and i.v. ganciclovir can be used as second line of therapy (Ljungman et al. 2008). The development of new antiviral drugs seems very promising, because some of them are able to prevent immunopathogical events triggered by the virus. In addition, they are unlike those targeted CMV DNA polymerase and therefore, suppress active viral replication but do not eliminate the virus (Ducancelle et al. 2004). Maribavir, CMV UL97 kinase inhibitor, does not target DNA polymerase, is considered one of the most promising anti CMV drugs in clinical development. Lobucavir, adefovir-dipivoxil and antisense oligonucleotides are under clinical development (Vancíková and Dvorák 2001). Table 15.2 demonstrates some of the recommendations for the management of CMV diseases in immunocompromised hosts.

Adoptive immunoprophylaxis. It is not standardized for routine use. Several groups have studied the usefulness of adoptive transfer of CMV-specific T cells or vaccination with CMV-primed DC (dendritic cells) (Ljungman et al. 2008). These technologies seem not to be associated with significant toxicity but their effectiveness needs to be further assessed in controlled trials.

Anti CMV Drug Resistance

Antiviral drug-resistant CMV mostly emerges in highly immunocompromised patients such those with AIDS and bone marrow or solid

Table 15.2 Treatment of CMV infection/disease in immunocompromised host

Drug	MOA	Dose	Beneficial role
Ganciclovir (GCV)	Nucleoside analogue	Induction: 5 mg/kg q 12h i.v. , 2–3 weeks, then for pts at risk of relapse 6 mg/kg once a day i.v. for 5 days per week Immunoglobulin (500 mg/kg) every other day for first 2 weeks, then weekly for pneumonia	Prophylaxis, preemptive therapy and treatment of CMV disease
Valganciclovir	Nucleoside analogue	Oral: 900 mg /day for 3 weeks	Prophylaxis, preemptive and treatment of CMV disease
Cidofovir	Nucleoside analogue	i.v. 5 mg/kg infusion once/week for 2 weeks. Then 3 mg/kg once every 2 weeks	Poor results for preemptive therapy and treatment of CMV disease, nephrotoxic
Foscarnet	Pyrophosphate analogue	Induction: 60 mg/kg q 12 h i.v. Maintenance: 90 mg/kg once a day i.v. for 5 days per week for 3 weeks	Second line for preemptive therapy or treatment of CMV disease in case of resistance to GCV or neutropenia

Reusser (2002)

organ recipients with a high systemic CMV load (Drew 2000). Drug-resistant CMV infections have rarely been reported in other clinical settings. However, Erice et al. (1989) highlighted the risk of drug-resistant CMV emerging in patients with blood malignancies. These authors were the first to describe ganciclovir-resistant isolates and one of these isolates was recovered from a patient with chronic lymphocytic leukaemia. Rise in the viral load during first week of antiviral therapy is not an indication of viral resistance (Ljungman et al. 2008), but usually does emerge after several weeks of antiviral therapy. Drug resistance might be clinical or viral. Clinical resistance depends on host factors, but viral resistance is due to mutations in the viral genome. The simultaneous recurrence of multiple strains has been observed in immunocompromised patients (Baldanti et al. 1998). The presence of antiviral resistance can be determined by either phenotypic or genotypic assay. DNA sequencing can be used to screen for the most commonly seen mutations in ganciclovir-resistant strains of CMV (Ljungman et al. 2008). Such assays should be performed to allow selection of correct second line antiviral therapy. Understanding how the CMV genotype changes in the presence of antiviral therapy changes will help to determine the best strategy for long-term anti-CMV treatment.

References

Baldanti F, Simoncini L, Sarasini A, Zavattoni M, Grossi P, Revello MG, Gerna G (1998) Ganciclovir resistance as a result of oral ganciclovir in a heart transplant recipient with multiple human cytomegalovirus strains in blood. Transplantation 66:324–329

Bauer CC, Jaksch P, Aberle SW, Haber H, Lang G, Klepetko W, Hofmann H, Puchhammer-Stöckl E (2007) Relationship between cytomegalovirus DNA load in epithelial lining fluid and plasma of lung transplant recipients and analysis of coinfection with Epstein-Barr virus and human herpesvirus 6 in the lung compartment. J Clin Microbiol 45:324–328

Chemaly RF, Torres HA, Hachem RY, Nogueras GM, Aguilera EA, Younis A, Lina MA, Rodriguez G, Tarrand JJ, Raad II (2005) Cytomegalovirus pneumonia in patients with lymphoma. Cancer 104:1213–1220

Church J, Goyals S, Tyagi AK, Scott RAH, Stavrou P (2007) Cytomegalovirus retinitis in chronic lymphocytic leukemia. Eye 21:1230–1233

Cvetković RS, Wellington K (2005) Valganciclovir: a review of its use in the management of CMV infection and disease in immunocompromised patients. Drugs 65:859–878

Drew WL (1992) Cytomegalovirus infection in patients with AIDS. Clin Infect Dis 14:608–615

Drew WL (2000) Ganciclovir resistance: a matter of time and titre. Lancet 356:609–610

Ducancelle A, Belloc S, Alain S, Scieux C, Malphettes M, Petit F, Brouet JC, Marie-Le Pors MJC, Mazeron MC (2004) Comparison of sequential cytomegalovirus isolates in a patient with lymphoma and failing antiviral therapy. J Clin Virol 29:241–247

Erice A, Chou S, Biron K, Stanat SC, Balfour HH, Jordan JC (1989) Progressive disease due to ganciclovir-resistant cytomegalovirus in immunocompromised patients. N Engl J Med 320:289–293

Faderl S, Thomas DA, O'Brien S, Garcia-Manero G, Kantarjian HM, Giles FJ, Koller C, Ferrajoli A, Verstovsek S, Pro B, Andreeff M, Beran M, Cortes J, Wierda W, Tran N, Keating MJ (2003) Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood 101:3413–3415

Grigoleit GU, Kapp M, Hebart H, Fick K, Beck R, Jahn G, Einsele H (2007) Dendritic cell vaccination in allogeneic stem cell recipients: induction of human cytomegalovirus (HCMV)-specific cytotoxic T lymphocyte responses even in patients receiving a transplant from an HCMV-seronegative donor. J Infect Dis 196:699–704

Han XY (2007) Epidemiologic analysis of reactivated cytomegalovirus antigenemia in patients with cancer. J Clin Microbiol 45:1126–1132

Ikewaki J, Ohtsuka E, Kawano R, Ogata M, Kikuchi H, Nasu M (2003) Real-time PCR assay compared to nested PCR and antigenemia assays for detecting cytomegalovirus reactivation in adult T-cell leukemia-lymphoma patients. J Clin Microbiol 41:4382–4387

Jain M, Duggal S, Chugh TD (2011) Cytomegalovirus infection in non-immunosuppressed critically ill patients. J Infect Dev Ctries 5:571–579

Jones GR, Konsler GK, Dunaway RP, Pusek SN (1996) Infection risk factors in febrile, neutropenic children and adolescents. J Pediatr Hematol Oncol 13:217–229

Koh AY, Pizzo PA (2011) Infectious complications in pediatric cancer patients. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology, 6th edn. Lippincott Williams & Wilkins, Philadelphia, p 1190

Ljungman P, Griffiths P, Paya C (2002) Definitions of cytomegalovirus infection and disease in transplant recipients. Clin Infect Dis 34:1094–1097

Ljungman P, de la Camara R, Cordonnier C, Einsele H, Engelhard D, Reusser P, Styczynski J, Ward K (2008) Management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT. Bone Marrow Transplant 42:227–240

Loutfy SA, Mansout MT (2000) Cytomegalovirus infection in immunocompromised cancer patients: immunovirological study. PhD thesis, National Cancer Institute, Cairo University, Egypt

Loutfy SA, Ibrahim MF, El-Wakil M, Moneer MM (2010) Presence of Human Herpes virus 6 (HHV6) in pediatric lymphomas: impact on clinical course and association with cytomegalovirus infection. Virol J 7:287

Madi N, Al-Nakib W, Mustafa AS, Saeed T, Pacsa A, Nampoory MR (2007) Detection and monitoring of cytomegalovirus infection in renal transplant patients by quantitative real-time PCR. Med Princ Pract 16:268–273

Meyers JD, Ljungman P, Fisher LD (1990) Cytomegalovirus excretion as a predictor of cytomegalovirus disease after marrow transplantation: importance of cytomegalovirus viremia. J Infect Dis 162:373–380

Nguyen Q, Estey E, Raad I, Rolston K, Kantarjian H, Jacobson K, Konoplev S, Ghosh S, Luna M, Tarrand J, Whimbey E (2001) Cytomegalovirus pneumonia in adults with leukemia: an emerging problem. Clin Infect Dis 32:539–545

Razonable RR, Paya CV, Smith TF (2002) Role of the laboratory in diagnosis and management of cytomegalovirus infection in hematopoietic stem cell and solid-organ transplant recipients. J Clin Microbiol 40:746–752

Reusser P (2002) Management of viral infections in immunocompromised cancer patients. Swiss Med Wkly 132:374–378

Staras SA, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ (2006) Seroprevalence of cytomegalovirus infection in the United States 1988-1994. Clin Infect Dis 43:1143–1151

Sinclair J, Sissons P (2006) Latency and reactivation of human cytomegalovirus. J Gen Virol 87(Pt 7):1763–1779

Torres HA, Kontoyiannis DP, Aguilera EA, Younes A, Luna MA, Tarrand JJ, Nogueras GM, Raad II, Chemaly RF (2006) Cytomegalovirus infection in patients with lymphoma: an important cause of morbidity and mortality. Clin Lymphoma Myeloma 6:393–398

Torres HA, Aguilera E, Safdar A, Rohatgi N, Raad II, Sepulveda C, Luna M, Kontoyiannis DP, Chemaly RF (2008) Fatal cytomegalovirus pneumonia in patients with hematological malignancies: an autopsy-based case-control study. Clin Microbiol Infect 14:1160–1166

Vancíková Z, Dvorák PC (2001) Cytomegalovirus infection in immunocompetent and immunocompromised individuals – a review. Curr Drug Immune Endocr Metabol Disord 1:179–187

Wade JC (2006) Viral infections in patients with hematological malignancies. Hematology Am Soc Hematol Educ Program: 368–374

Wang F, Yao K, Yin QZ, Zhou F, Ding CL, Peng GY, Xu J, Chen Y, Feng DJ, Ma CL, Xu WR (2006) Human herpesvirus-6 specific interleukin 10-producing CD4+ T cells suppress the CD4+ T-cell response in infected individual. Microbiol Immunol 50:787–803

Wang YC, Wang NC, Lin JC, Perng CL, Yeh KM, Yang YS, Chiu CH, Chang FY (2011) Risk factors and outcomes of cytomegalovirus viremia in cancer patients: a study from a medical center in northern Taiwan. J Microbiol Immunol Infect 44:442–448

Yee-Guardino S, Gowans K, Yen-Lieberman B, Berk P, Kohn D, Wang FZ, Danziger-Isakov L, Sabella C, Worley S, Pellett PE, Goldfarb J (2008) Beta-herpesviruses in febrile children with cancer. Emerg Infect Dis 14:579–585

Yeung SCJ, Escalante CP, Gagel RF (2009) Pneumonia in cancer patients. In Medical Care of Cancer Patients. Sai-Ching Jim Y, Carmen PE, Robert FG. 1st ed, BC Decker Inc. Texas, pp 331. patients. J Clin Microbiol 30:527–530